**TITLE PAGE**

# Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum

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**Short title:** Candesartan across the ejection fraction spectrum

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**ABSTRACT**

**Aims:**

We tested the hypothesis that candesartan improves outcomes in heart failure with mid-range ejection fraction (HFmrEF, EF 40-49%).

**Methods and Results:**

In 7598 patients enrolled in the CHARM Programme (HF across the spectrum of EF), we assessed characteristics, outcomes and treatment effect of candesartan according to EF.

Patients with HFmrEF (n=1322; 17%) were similar to those with HFrEF (n=4323; 57%) with respect to some characteristics, and intermediate between HFrEF and HFpEF (n=1953; 26%) with respect to others. Over 2.9 years mean follow-up, the incidence rates for the primary outcome of cardiovascular death or HF hospitalization were 15.9, 8.5 and 8.9 per 100-patient years in HFrEF, HFmrEF and HFpEF. In adjusted analyses, the rates of the primary outcome declined with increasing EF up to 50%.

For treatment effect, the incidence rates for the primary outcome for candesartan vs. placebo were in HFrEF: 14.4 vs. 17.5 per 100 patient-years (hazard ratio [95% confidence interval] 0.82 [0.75-0.91], p<0.001); in HFmrEF: 7.4 vs. 9.7 per 100 patient-years (0.76 [0.61-0.96] p=0.02); and in HFpEF: 8.6 vs. 9.1 per 100 patient-years (0.95 [0.79-1.14] p=0.57). For recurrent HF hospitalization, the incidence rate ratios were in HFrEF: 0.68 (0.58-0.80), p<0.001; in HFmrEF: 0.48 (0.33-0.70), p<0.001; and in HFpEF: 0.78 (0.59-1.03), p=0.08. With EF as a continuous spline variable, candesartan significantly reduced the primary outcome until EF well over 50% and recurrent HF hospitalizations until EF well over 60%.

**Conclusion:**

Candesartan improved outcomes in HFmrEF to a similar degree as in HFrEF.

**Key words:** Heart Failure; Mid-Range Ejection Fraction; Preserved Ejection Fraction; Outcomes; Candesartan; Angiotensin Receptor Blocker; Randomized Controlled Trial

**Clinicaltrials.gov:**

CHARM Alternative NCT00634400

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## INTRODUCTION

The 2016 European Society of Cardiology heart failure (HF) guidelines recognized the gap in evidence for patients with HF and ejection fraction (EF) in the middle range of 40-49% (HFmrEF) between HF with reduced (HFrEF; <40%) and preserved (HFpEF; ≥50%) EF (1, 2). Emerging data from registry and cohort settings are inconsistent regarding whether clinical characteristics in HFmrEF may be more similar to in HFrEF or HFpEF or intermediate (3-10). Little is known regarding cause-specific outcomes, which may be especially important for testing existing or developing novel interventions for HFmrEF. Finally, although EF in HFmrEF is not normal, there is currently no evidence based therapy in this EF category.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Programme studied patients with symptomatic heart failure across the spectrum of EF and represents an opportunity to assess the characteristics, outcomes and efficacy of angiotensin receptor blockade across the entire EF spectrum. In CHARM, Increasing EF was associated with better outcomes until approximately 45%, without further improvement at higher EFs (11). In CHARM-Preserved, which enrolled patients with LVEF >40%, candesartan did not significantly reduce cardiovascular death or HF hospitalization (unadjusted hazard ratio 0.89 [95% CI 0.77–1.03], p=0.118; covariate adjusted 0.86 [0.74–1.0], p=0.051). However, it was effective in HFrEF, and in CHARM-Overall, there was no heterogeneity with respect to EF (p=0.33). The potential benefit in the HFmrEF range has not been specifically reported (12). We used data from the CHARM Programme to assess the relationship between EF and patient characteristics and outcomes, and tested the hypothesis that candesartan improves outcomes in HFmrEF.

## METHODS

### Patients

The rationale and design (13) and main outcomes (12) of the CHARM Programme have been described. Briefly, 7599 patients with symptomatic HF were randomized to candesartan vs. placebo

in 3 separate trials, CHARM-Added (EF ≤40% treated with an ACE-inhibitor, n=2548), CHARM-Alternative (EF ≤40% intolerant to an ACE-inhibitor, n=2028), and CHARM-Preserved (EF >40%, 19% treated with an ACE-inhibitor, n=3023). For the present analysis, the 7598 patients with available integer digit EF were divided into HFrEF, EF<40%; HFmrEF, EF 40-49%; and HFpEF, EF≥50%.

The primary outcome was time to cardiovascular (CV) death or first HF hospitalization. Additional pre-specified outcomes included times to first HF hospitalization, all-cause hospitalization, CV death, and all-cause death, and rate of recurrent heart failure hospitalizations.

**Statistical methods**

Baseline characteristics across the 3 EF groups were summarized using means and standard deviations or medians (interquartile ranges) for continuous data, or percentages for categorical data, respectively. Trend tests were performed across EF groups using linear regression for continuous and chi square tests for categorical data.

The association between EF and outcomes was assessed in the overall population (irrespective of treatment assignment) with EF as 3 categories and as a continuous independent variable, and outcomes as the dependent variable. For associations between EF and outcomes, incidence rates per 100 patient-years were calculated for each outcome in each EF group. The associations between EF groups and all time to first outcomes were assessed with univariable and multivariable Cox regressions and between EF groups and rates of recurrent HF hospitalizations using univariable and multivariable negative binomial regression models which take both time to and number of events into account. The multivariable Cox models violated the proportional hazards assumption; therefore stratified models using age, treatment assignment and body mass index deciles were entered as stratification factors, after which the proportional hazards assumption was no longer violated. The adjusted associations between EF as a continuous variable and outcomes were plotted using multivariable restricted cubic splines models with 5 knots, using Poisson

regression models to estimate incidence rates for time to first event outcomes and using negative binomial regression for the recurrent HF hospitalizations outcome.

The effect of candesartan vs. placebo was assessed in the 3 EF categories and in the overall population with EF as a continuous variable. Incidence rate ratios were calculated for candesartan vs. placebo for each outcome within each EF group. The interactions between treatment and EF category were also examined using Cox models. Within EF categories, the effect of candesartan on time to the primary composite outcome was assessed with Kaplan-Meier analysis, for the primary and 4 additional time to first event outcomes from the original CHARM Programme with univariable Cox regressions, and for the recurrent outcome using univariable negative binomial regression. For EF as a continuous variable, the effect of candesartan was modeled using univariable restricted cubic splines with 3 knots, using Poisson regression for time to first outcomes and negative binomial regressions for the recurrent outcome.

Patients lost to follow-up (n=10) were censored alive at last follow-up. Statistical analyses were performed in Stata v. 14 (College Station, USA). The CHARM Programme was approved by local ethics boards. All patients provided written informed consent.

## RESULTS

### EF and baseline characteristics

Of 7599 patients enrolled in CHARM, EF was available in 7598 patients with 4323 (57%) patients falling into the HFrEF range, 1322 patients (17%) falling into the HFmrEF range, and 1953 patients (26%) falling into the HFpEF range. HFmrEF resembled HFrEF regarding most characteristics including age, systolic blood pressure, percent women, previous myocardial infarction, and atrial fibrillation (**Table 1**). HFmrEF was intermediate between HFrEF and HFpEF with regard to history of hypertension, distribution of NYHA class, and body mass index (p for trend over EF categories <0.001 for all). Some characteristics, such as diabetes mellitus (p for trend =0.71), were similarly prevalent in all 3 EF categories.

**EF and outcomes (irrespective of treatment assignment)**

**Table 2** shows event rates and unadjusted and adjusted hazard ratios for time to event outcomes and incidence rate ratios for the recurrent outcome for each of the 3 EF groups (irrespective of treatment assignment). Over a mean follow-up of 2.9 years overall, there were 15.9, 8.5, and 8.9 primary events (cardiovascular death or first HF hospitalization) per 100 patient-years in HFrEF, HFmrEF, and HFpEF, respectively; and 20.0, 10.8, and 11.1 recurrent HF hospitalizations per 100 patient-years, respectively. The incidence rates for the first HF hospitalization, CV death and all-cause death were similar in patients with HFmrEF and those with HFpEF, and considerably lower than in those with HFrEF. The incidence of all-cause hospitalization was somewhat lower in HFmrEF than in HFrEF and HFpEF.

**Figure 1** shows adjusted incidence rates for each outcome according to continuous EF. For the primary, CV death, and all-cause death outcomes, the risk decreased steeply with increasing EF until EF around 50%, and the risk was flat thereafter. For first HF hospitalization, first all-cause hospitalization and recurrent HF hospitalization, the risk decreased with increasing EF until EF around 40%. The p overall and p for non-linearity for EF and all outcomes were <0.001.

**EF and candesartan treatment effect**

**Figure 2** shows Kaplan-Meier curves with time to the primary outcome for each of the 3 EF groups. Candesartan showed a beneficial effect compared to placebo in HFrEF and HFmrEF but not in HFpEF. **Table 3** shows event rates and unadjusted hazard ratios and incidence rate ratios for each outcome in each EF group according to treatment assignment. In HFrEF and HFmrEF, candesartan significantly reduced the primary composite outcome, first HF hospitalization and recurrent HF hospitalization. In HFrEF, candesartan also significantly reduced CV death and all-cause death. In HFpEF, candesartan did not significantly reduce any outcome, but for recurrent HF hospitalizations, the hazard ratio (HR) (95% confidence interval [CI]) was 0.78 (0.59-1.03, p=0.08). There was no

significant interaction between EF group and treatment in the association between treatment and outcomes, except for the all-cause death outcome.

**Figure 3** shows unadjusted treatment effects for each outcome according to continuous EF. The hazard ratios and upper 95% CIs were always below 1.0, indicating benefit with candesartan, up to and beyond EF~50% for the primary composite and first HF hospitalization outcomes, and up to EF~60% for the recurrent HF hospitalizations outcome. Candesartan reduced each of CV death, all-cause death and all-cause hospitalization only at the lower end of the EF spectrum.

## DISCUSSION

In this large and long-term clinical trial programme of patients with heart failure including ejection fractions across the entire spectrum, we found that 1) HFmrEF resembled HFrEF with respect to many baseline characteristics, including age, gender and history of myocardial infarction; 2) that HFmrEF resembled HFpEF with respect to lower risk of HF and CV events; and 3) that candesartan reduced the composite of CV death and HF hospitalization, as well as first and recurrent HF hospitalizations, in HFrEF and HFmrEF but not in HFpEF, although there was no statistical interaction between EF category and candesartan treatment effect.

We recognize, along with others, that EF is not an optimal classifier in HF (1, 14), that cut-offs are arbitrary, and that other tools to identify disease specific phenotypes may emerge as more important than EF. But EF remains the most commonly used classifier. Clinical trials, drug labels, treatment guidelines, and reimbursement schemes are based on EF cut-offs (15). EF may change with treatment and over time, but this appears highly variable depending on setting and baseline treatment (3, 10, 16). HFmrEF constitutes up to 20% of the HF population (4, 17). Thus, whether a separate phenotype or part of a continuum, HFmrEF is common, and data regarding patient characteristics and outcomes and response to therapy are clinically relevant and relevant for trial design.

The boundary for "normal EF" remains controversial but the EchoNoRMAL study suggested a lower limit of 49-57%, depending on age, sex and ethnicity(18). According to the American Society of Echocardiography and European Association of Cardiovascular Imaging, the normal EF and normal range (±2 standard deviations) is 62% (52-72%) in men and 64% (54-74%) in women(19). In HF, the EF distribution was bimodal in the OPTIMIZE-HF Registry (20) and in Olmsted County (21) but unimodal and normally distributed in CHARM (11). Regardless of distribution, most studies have consistently shown that patients with EF in the 40-50% range constitute up to 20% of the HF population(4, 11, 17, 20, 21). Thus HFmrEF is not infrequently encountered in clinical settings.

**EF and baseline characteristics**

HFmrEF is often termed "intermediate" but our findings challenge this. Some baseline characteristics in HFmrEF were intermediate between HFrEF and HFpEF. However, HFmrEF distinctly resembled HFrEF in several important aspects, including age, sex and ischæmic heart disease and history of myocardial infarction, consistent with other emerging analyses (8). With improved and earlier treatment for myocardial infarction, the importance of the HFmrEF category may also be increasing over time. While diabetes was equally common in all EF categories it may contribute differently to HF, by contributing to ischemic heart disease and myocardial infarction in lower EF and together with obesity and other comorbidities potentially to microvascular inflammation, fibrosis and diastolic dysfunction in higher EF (22, 23).

**EF and outcomes**

Prior studies have described the association of EF with outcomes in HF: the risk for cardiovascular outcomes declined as EF increased up to 45% in the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)(24) and up to 40% in a previous analysis from CHARM(11). In the present analysis, crude CV event rates were similar in HFmrEF and HFpEF and much lower than in HFrEF; and analogously, the adjusted hazard ratios demonstrated lower risk in HFmrEF and HFpEF

compared to HFrEF. However, regarding the importance of incremental *increases* in EF, the HFmrEF group was similar to HFrEF in that an increasing EF was associated with improving prognosis (up-sloping curves in spline analyses in Figure 1 up to EF ~50%), whereas within the HFpEF group, changes in EF were not related to prognosis (flat curves). This is also consistent with the risk of non-CV events, particularly all-cause hospitalization, increasing with the highest EF, where comorbidity and frailty may be drivers of both deconditioning and HF symptoms (which may be difficult to interpret and in trials may have led to inclusion of patients without HF), as well as non-CV outcomes.

**EF and candesartan treatment effect**

Across the entire EF spectrum and for all outcomes, there was no significant interaction between EF and treatment effect. Nevertheless, given the different effect in the separate HFrEF and HFpEF trials in CHARM, extensive trial data that have been positive in HFrEF and neutral in HFpEF, and new designation of HFmrEF, this post-hoc analysis of pre-specified EF strata was considered justified, novel, and important.

We found that in HFrEF and HFmrEF candesartan appeared to significantly reduce the primary composite of time to CV death or HF hospitalization and time to HF hospitalization, as well as the novel outcome recurrent HF hospitalization, with hazard ratios and incidence rate ratios similar in HFrEF and HFmrEF and clinically meaningful approximately 20% reductions in time to first CV events and more than 30% reductions in recurrent HF hospitalization. However, since event rates were lower in HFmrEF than in HFrEF, the absolute risk reductions will also be lower in HFmrEF than in HFrEF. Spline analyses with EF as a continuous variable confirmed these findings, with candesartan efficacy constant at lower EFs and generally beginning to decline as EF moved above 50%. In PARADIGM-HF (HFrEF defined as EF ≤40%), the beneficial effect of sacubitril/valsartan was similar regardless of EF (25). This is consistent with our observations of a similar treatment effect of candesartan regardless of EF up to ~50% (flat sections of curves in Figure 3). In TOPCAT, spironolactone was not effective in HFpEF defined as EF ≥45%, but there was a suggestion of

potential efficacy with lower EF and declining efficacy with increasing EF(26); this is consistent with our observations of declining effect of candesartan with increasing EF in and above the HFmrEF range (upsloping sections of curves in Figure 3). The present findings now demonstrate HF treatment efficacy in the HFmrEF range. These findings raise the possibility that the arbitrary EF 35% or 40% cut-offs used in many previous and trials may have excluded patients who would potentially have derived benefit from the many interventions proven to be effective in HFrEF.

**Limitations**

The sample size of 7958 provided convincing efficacy results for the lower EF spectrum and narrow confidence intervals throughout a broad EF spectrum. However, at the extremes of EF statistical power was limited. Multiple outcomes and testing as well as the post-hoc nature of this analysis increase the risk that some of the findings may have occurred by chance. EF may change over time and there is inherent variability in EF measurements but this is likely in both directions without systematic bias, and with this large sample size, the consequences of measurement error are reduced. There is an even-digit bias in assigning EF and unconventional, uneven, EF categories, may reduce the risk of systematic miss-classification (28). However, with existing trial cut-off and our focus specifically on the newly designated HFmrEF category, we conducted our analyses using even digit cut-offs.

**Conclusion**

HFmrEF resembled HFrEF with regard to some characteristics and was intermediate with regard to others. HFmrEF resembled HFpEF with regard to risk of CV and HF outcomes, which was lower than in HFrEF. Importantly, candesartan improved outcomes in the HFmrEF range. This finding should be interpreted with caution because this was a post-hoc analysis and there was no statistical interaction between EF category and candesartan treatment. Thus whether patients in the

HFmrEF range might benefit from therapies shown to be effective in HFrEF must be considered a hypothesis only.

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**Conflicts of interest:**
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PSJ: none
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**FIGURE LEGENDS**

**Figure 1. Association between EF as a continuous variable and outcomes (regardless of treatment assignment).** Adjusted Incidence rates (per 100 patient-years) and 95% confidence intervals for the 6 outcomes according to EF as a continuous variable. Adjusted for the same variables as in Table 2. The range shaded blue is the HFmrEF range.

**Figure 2. Effect of candesartan on the primary outcome by EF category.** Kaplan-Meier time-to-event curves for candesartan (red) vs. placebo (blue) for the primary composite outcome: time to cardiovascular death or first heart failure hospitalization, for the 3 EF categories. Large graphs show y-axis up to 1.0; inserted graphs show y-axis up to 0.4.

**Figure 3. Effect of candesartan on all outcomes by EF as a continuous variable.** Unadjusted incidence rate ratios and 95% confidence intervals for the candesartan treatment effect for the 6 outcomes according to EF as a continuous variable. The range shaded blue is the HFmrEF range. The red arrow indicates the EF at which the 95% confidence interval for the hazard ratio for candesartan vs. placebo was no longer < 1.0.

**TABLES**

**Table 1. Baseline characteristics according to EF category**

| Variable name | EF <40%, HFrEF n=4323 (57%) | HFmrEF, EF 40-49% n=1322 (17%) | EF ≥50%, HFpEF n=1953 (26%) | *p for trend** |
|---|---|---|---|---|
| Candesartan | 2155 (49.8%) | 667 (50.5%) | 980 (50.2%) | 0.77 |
| **Clinical** | | | | |
| Age (years) | 65 ± 11 | 65 ± 11 | 67 ± 11 | 0.001 |
| Female | 1116 (25.8%) | 395 (29.9%) | 888 (45.5%) | <0.001 |
| Race | | | | 0.035 |
| European | 3865 (89.4%) | 1237 (93.6%) | 1767 (90.5%) | |
| Black | 194 (4.5%) | 43 (3.3%) | 89 (4.6%) | |
| Other | 264 (6.1%) | 42 (3.2%) | 97 (5.0%) | |
| NYHA | | | | <0.001 |
| II | 1460 (33.8%) | 763 (57.7%) | 1193 (61.1%) | |
| III | 2713 (62.8%) | 550 (41.6%) | 721 (36.9%) | |
| IV | 150 (3.5%) | 9 (0.7%) | 39 (2.0%) | |
| EF | 30 (23, 35) | 44 (41, 46) | 58 (53, 63) | <0.001 |
| BMI | 27.1 (24.1, 30.3) | 27.8 (25.0, 31.2) | 28.6 (25.4, 32.6) | <0.001 |
| SBP, mm Hg | 126 (112, 140) | 130 (120, 145) | 140 (124, 150) | <0.001 |
| DBP, mm Hg | 76 (70, 80) | 80 (70, 85) | 80 (70, 85) | <0.001 |
| Physical exam edema | 968 (22.4%) | 306 (23.2%) | 579 (29.6%) | <0.001 |
| Creatinine, mg/dl | 1.21 ± 0.85 | 1.16 ± 0.43 | 1.11 ± 0.41 | 0.001 |
| HF cause | | | | |
| Ischemic | 2810 (65.0%) | 885 (66.9%) | 985 (50.4%) | <0.001 |
| Idiopathic | 1017 (23.5%) | 173 (13.1%) | 137 (7.0%) | <0.001 |
| Hypertensive | 275 (6.4%) | 168 (12.7%) | 538 (27.5%) | <0.001 |
| **Medical History** | | | | |
| Previous HF | 3189 (73.8%) | 926 (70.0%) | 1310 (67.1%) | <0.001 |
| MI | 2520 (58.3%) | 761 (57.6%) | 722 (37.0%) | <0.001 |
| Angina pectoris | 2388 (55.2%) | 813 (61.5%) | 1150 (58.9%) | 0.001 |
| CABG | 1075 (24.9%) | 336 (25.4%) | 380 (19.5%) | <0.001 |
| PCI | 659 (15.2%) | 241 (18.2%) | 328 (16.8%) | 0.06 |
| Stroke | 376 (8.7%) | 123 (9.3%) | 164 (8.4%) | 0.8 |
| DM | 1236 (28.6%) | 378 (28.6%) | 549 (28.1%) | 0.71 |
| Hypertension | 2100 (48.6%) | 743 (56.2%) | 1342 (68.7%) | <0.001 |
| AF | 1132 (26.2%) | 339 (25.6%) | 612 (31.3%) | <0.001 |
| Pacemaker | 393 (9.1%) | 100 (7.6%) | 144 (7.4%) | 0.015 |
| Current Smoker | 668 (15.5%) | 210 (15.9%) | 236 (12.1%) | <0.001 |
| ICD | 160 (3.7%) | 21 (1.6%) | 10 (0.5%) | <0.001 |
| Cancer | 273 (6.3%) | 90 (6.8%) | 150 (7.7%) | 0.047 |
| **Medical treatment** | | | | |

| | | | | |
|---|---|---|---|---|
| ACE-inhibitor | 2446 (56.6%) | 359 (27.2%) | 320 (16.4%) | <0.001 |
| ß-blocker | 2385 (55.2%) | 763 (57.7%) | 1055 (54.0%) | 0.61 |
| Diuretic | 3831 (88.6%) | 984 (74.4%) | 1470 (75.3%) | <0.001 |
| Spironolactone | 889 (20.6%) | 151 (11.4%) | 232 (11.9%) | <0.001 |
| Digitalis | 2296 (53.1%) | 465 (35.2%) | 492 (25.2%) | <0.001 |
| Calcium antagonist | 544 (12.6%) | 319 (24.1%) | 678 (34.7%) | <0.001 |
| Other vasodilator | 1713 (39.6%) | 524 (39.6%) | 726 (37.2%) | 0.080 |
| Oral anticoagulant | 1525 (35.3%) | 327 (24.7%) | 485 (24.8%) | <0.001 |
| Antiarrhythmic | 552 (12.8%) | 150 (11.3%) | 191 (9.8%) | <0.001 |
| Aspirin | 2335 (54.0%) | 816 (61.7%) | 1095 (56.1%) | 0.022 |
| Other antiplatelet | 181 (4.2%) | 61 (4.6%) | 113 (5.8%) | 0.006 |
| Lipid-lowering | 1782 (41.2%) | 591 (44.7%) | 779 (39.9%) | 0.59 |

Numbers are n (%), mean ± standard deviation, and median (interquartile range)
*p for trend over EF categories

NYHA, New York Heart Association
EF, ejection fraction
SD, standard deviation
BMI, body mass index
HF, heart failure
MI, myocardial infarction
CABG, coronary artery bypass graft
PCI, percutaneous coronary intervention
ICD, implantable cardioverter-defibrillator
ACE, angiotensin converting enzyme

**Table 2. Outcomes according to EF category (irrespective of treatment assignment)**

| | **EF <40% n=4323** | **EF 40-49% n=1322** | **EF >=50% n=1953** |
|---|---|---|---|
| Follow-up (years, mean ± SD) | 2.79 ± 1.02 | 2.93 ± 0.76 | 2.91 ± 0.70 |
| **CV Death + HF Hospitalization** | 1692 (39.2%)<br>15.9 (15.2-16.7)<br>per 100pyr | 305 (23.1%)<br>8.5 (7.6-9.5)<br>per 100pyr | 462 (23.7%)<br>8.9 (8.1-9.7)<br>per 100pyr |
| Unadjusted HR | 1.79 (1.61-1.98)<br>< 0.001 | 0.96 (0.83-1.11)<br>0.61 | Reference |
| Adjusted HR* | 1.58 (1.40-1.79)<br>< 0.001 | 1.00 (0.85-1.17)<br>0.98 | Reference |
| **HF Hospitalization** | 1115 (25.8%)<br>10.5 (9.9-11.1)<br>per 100pyr | 216 (16.3%)<br>6.0 (5.3-6.9)<br>per 100pyr | 343 (17.6%)<br>6.6 (5.9-7.3)<br>per 100pyr |
| Unadjusted HR | 1.58 (1.40-1.79)<br>< 0.001 | 0.92 (0.78-1.09)<br>0.34 | Reference |
| Adjusted HR* | 1.42 (1.23-1.64)<br>< 0.001 | 0.94 (0.78-1.13)<br>0.55 | Reference |
| **Recurrent HF Hospitalization, Incidence rate#** | 20.0 (19.2-20.8)<br>per 100pyr | 10.8 (9.8-11.9)<br>per 100pyr | 11.1 (10.2-12.0)<br>per 100pyr |
| Unadjusted incidence rate ratio | 2.14 (1.83-2.50)<br>< 0.001 | 1.04 (0.84-1.28)<br>0.71 | Reference |
| Adjusted IRR* | 1.96 (1.65-2.23)<br>< 0.001 | 1.21 (0.98-1.49)<br>0.07 | Reference |
| **CV Death** | 1079 (25.0%)<br>8.9 (8.4-9.5)<br>per 100pyr | 167 (12.6%)<br>4.3 (3.7-5.0)<br>per 100pyr | 214 (11.0%)<br>3.8 (3.3-4.3)<br>per 100pyr |
| Unadjusted HR | 2.37 (2.05-2.75)<br>< 0.001 | 1.15 (0.94-1.40)<br>0.19 | Reference |
| Adjusted HR* | 2.20 (1.85-2.61)<br>< 0.001 | 1.21 (0.98-1.51)<br>0.08 | Reference |
| **All-Cause Hospitalization** | 2802 (64.9%)<br>38.3 (37.0-39.8)<br>per 100pyr | 767 (58.1%)<br>31.0 (28.9-33.3)<br>per 100pyr | 1220 (62.5%)<br>35.4 (33.5-37.5)<br>per 100pyr |
| Unadjusted HR | 1.08 (1.01-1.15)<br>0.03 | 0.89 (0.81-0.97)<br>0.01 | Reference |
| Adjusted HR* | 0.99 (0.91-1.08)<br>0.85 | 0.89 (0.81-0.98)<br>0.02 | Reference |
| **All-Cause Death** | 1296 (30.0%)<br>10.7 (10.2-11.3)<br>per 100pyr | 209 (15.8%)<br>5.4 (4.7-6.2)<br>per 100pyr | 325 (16.6%)<br>5.7 (5.1-6.4)<br>per 100pyr |
| Unadjusted HR | 1.88 (1.66-2.12)<br>< 0.001 | 0.94 (0.79-1.12)<br>0.51 | Reference |
| Adjusted HR* | 1.73 (1.49-2.00)<br>< 0.001 | 0.98 (0.82-1.19)<br>0.88 | Reference |

Numbers are event rates (95% CI) per 100 patient-years or hazard ratios (95% CI)
*Adjusted for sex, ethnicity, New York Heart Association class, systolic blood pressure, heart failure cause (ischemic, idiopathic, hypertension), previous heart failure admission, atrial fibrillation, stroke, diabetes mellitus, smoking, and cancer, and stratified by Candesartan, age (years) and body mass

index (deciles). For recurrent HF model, candesartan, age, and BMI deciles were included as covariates.
#The recurrent event is based on number HF hospitalization episodes and not number of patients

SD, standard deviation
EF, ejection fraction
HR, hazard ratio
IRR, incidence rate ratio
CV, cardiovascular
HF, heart failure
pyr, patient-year

**Table 3. Treatment effect for 6 outcomes according to 3 EF categories**

| | Number and % of Participants with Events, and Incidence Rate per-100 person-year, HR (95%CI), *p*-values | | | | | |
|---|---|---|---|---|---|---|
| | **EF ≤ 40** | | **EF 40-49** | | **EF >=50** | |
| **CV Death + HF Hosp** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** |
| Incidence Rate | 906 (41.8%)<br>17.5 per 100pyr | 786 (36.5%)<br>14.4 per 100pyr | 168 (26.7%)<br>9.7 per 100pyr | 137 (20.5%)<br>7.4 per 100pyr | 235 (24.2%)<br>9.1 per 100pyr | 227 (23.2%)<br>8.6 per 100pyr |
| Unadjusted HR, *p* | 0.82 (0.75-0.91) *p<0.001* | | 0.76 (0.61-0.96) *p=0.02* | | 0.95 (0.79-1.14) *p=0.57* | |
| | *p* for interaction (EF group * treatment) = 0.27 | | | | | |
| **HF Hospitalization** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** |
| Incidence Rate | 617 (28.5%)<br>11.9 per 100pyr | 498 (23.1%)<br>9.1 per 100pyr | 122 (18.6%)<br>7.1 per 100pyr | 94 (14.1%)<br>5.1 per 100pyr | 178 (18.3%)<br>6.9 per 100pyr | 165 (16.8%)<br>6.3 per 100pyr |
| Unadjusted HR, *p* | 0.77 (0.68-0.86) *p<0.001* | | 0.72 (0.55-0.95) *p=0.02* | | 0.91 (0.74-1.13) *p=0.39* | |
| | *p* for interaction (EF group * treatment) = 0.23 | | | | | |
| **Recurrent HF Hosp** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** |
| Incidence Rate | 23.0 per 100yrs | 16.8 per 100yrs | 14.1 per 100yrs | 7.7 per 100yrs | 12.5 per 100yrs | 9.6 per 100yrs |
| Unadjusted IRR, *p* | 0.68 (0.58-0.80) *p<0.001* | | 0.48 (0.33-0.70) *p<0.001* | | 0.78 (0.59-1.03) *p=0.08* | |
| | *p* for interaction (EF group * treatment) = 0.60 | | | | | |
| **CV Death** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** |
| Incidence Rate | 578 (26.7%)<br>9.7 per 100pyr | 501 (23.5%)<br>8.2 per 100pyr | 90 (13.7%)<br>4.8 per 100pyr | 77 (11.5%)<br>3.9 per 100pyr | 101 (10.4%)<br>3.6 per 100pyr | 113 (11.5%)<br>4.0 per 100pyr |
| Unadjusted HR, *p* | 0.85 (0.75-0.96) *p=0.007* | | 0.81 (0.60-1.11) *p=0.19* | | 1.12 (0.85-1.46) *p=0.42* | |
| | *p* for interaction (EF group * treatment) = 0.10 | | | | | |
| **All-Cause Hospitalization** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** |
| Incidence Rate | 1417 (65.5%)<br>39.5 per 100pyr | 1385 (64.3%)<br>37.3 per 100pyr | 393 (60.0%)<br>33.1 per 100pyr | 374 (56.2%)<br>29.1 per 100pyr | 609 (62.7%)<br>35.8 per 100pyr | 611 (62.4%)<br>35.1 per 100pyr |
| Unadjusted HR, *p* | 0.95 (0.88-1.02) *p=0.18* | | 0.89 (0.78-1.03) *p=0.12* | | 0.98 (0.88-1.10) *p=0.78* | |
| | *p* for interaction (EF group * treatment) = 0.75 | | | | | |
| **All-Cause Death** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** | **Placebo** | **Candesartan** |
| Incidence Rate | 682 (31.5%)<br>11.4 per 100pyr | 614 (28.5%)<br>10.0 per 100pyr | 114 (17.4%)<br>6.0 per 100pyr | 90 (14.2%)<br>4.8 per 100pyr | 149 (15.3%)<br>5.3 per 100pyr | 176 (18.0%)<br>6.2 per 100pyr |
| Unadjusted HR, *p* | 0.88 (0.79-0.98) *p=0.02* | | 0.79 (0.60-1.04) *p=0.10* | | 1.18 (0.95-1.47) *p=0.14* | |
| | *p* for interaction (EF group * treatment) = 0.04 | | | | | |

Hosp, hospitalization
EF, ejection fraction
HR, hazard ratio
IRR, incidence rate ratio
CV, cardiovascular
HF, heart failure
pyr, patient-years

**FIGURES**

**Figure 1**

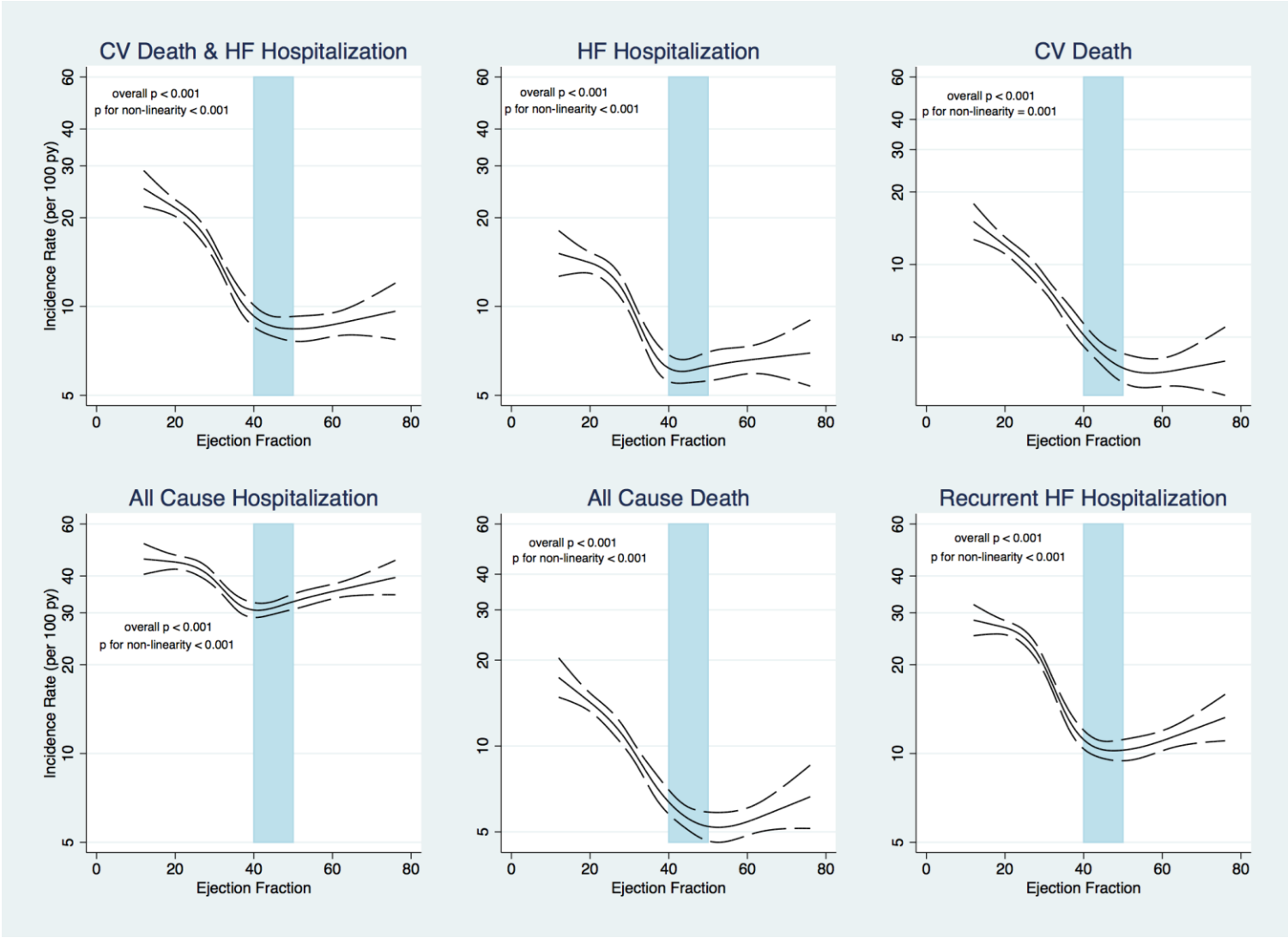


**Figure 2**

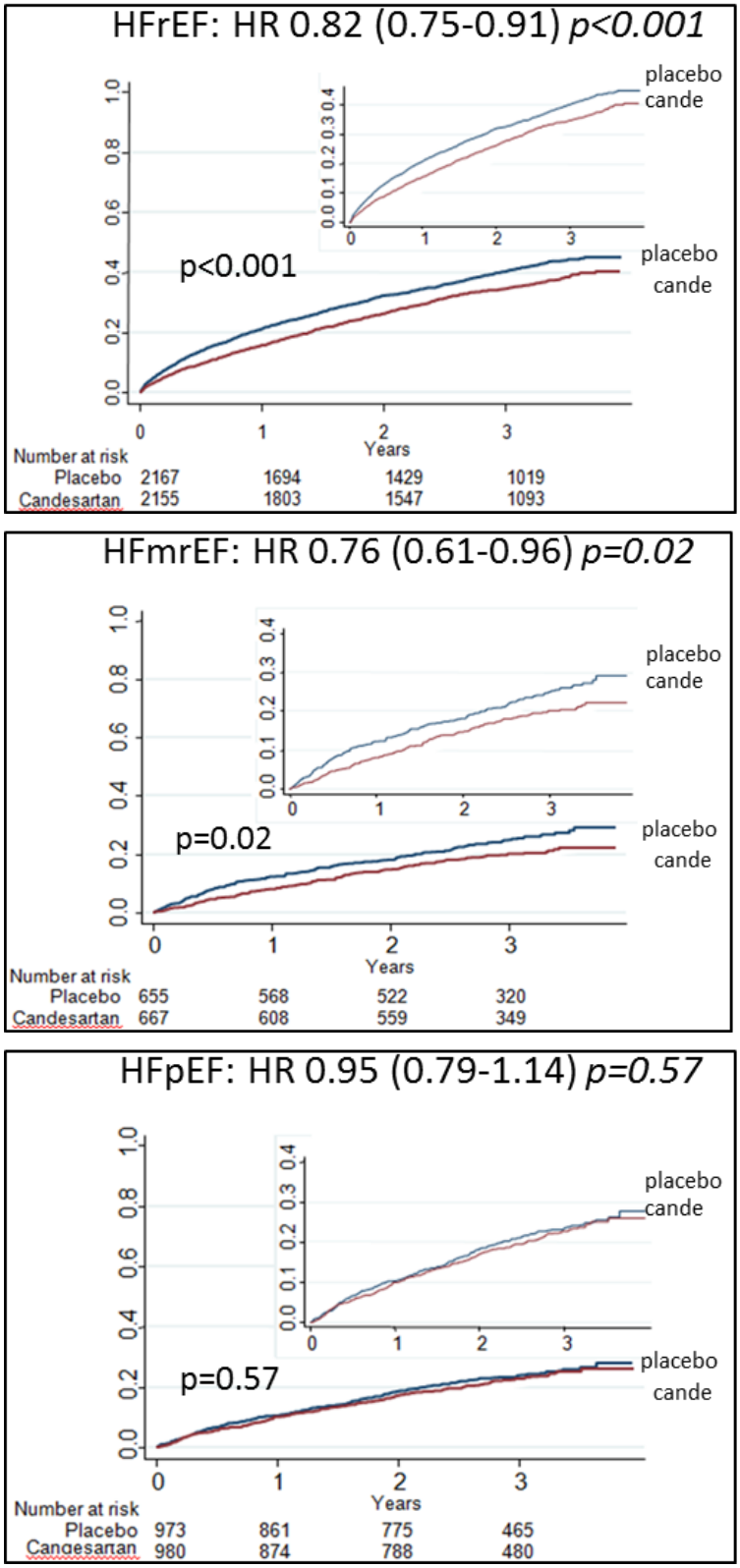
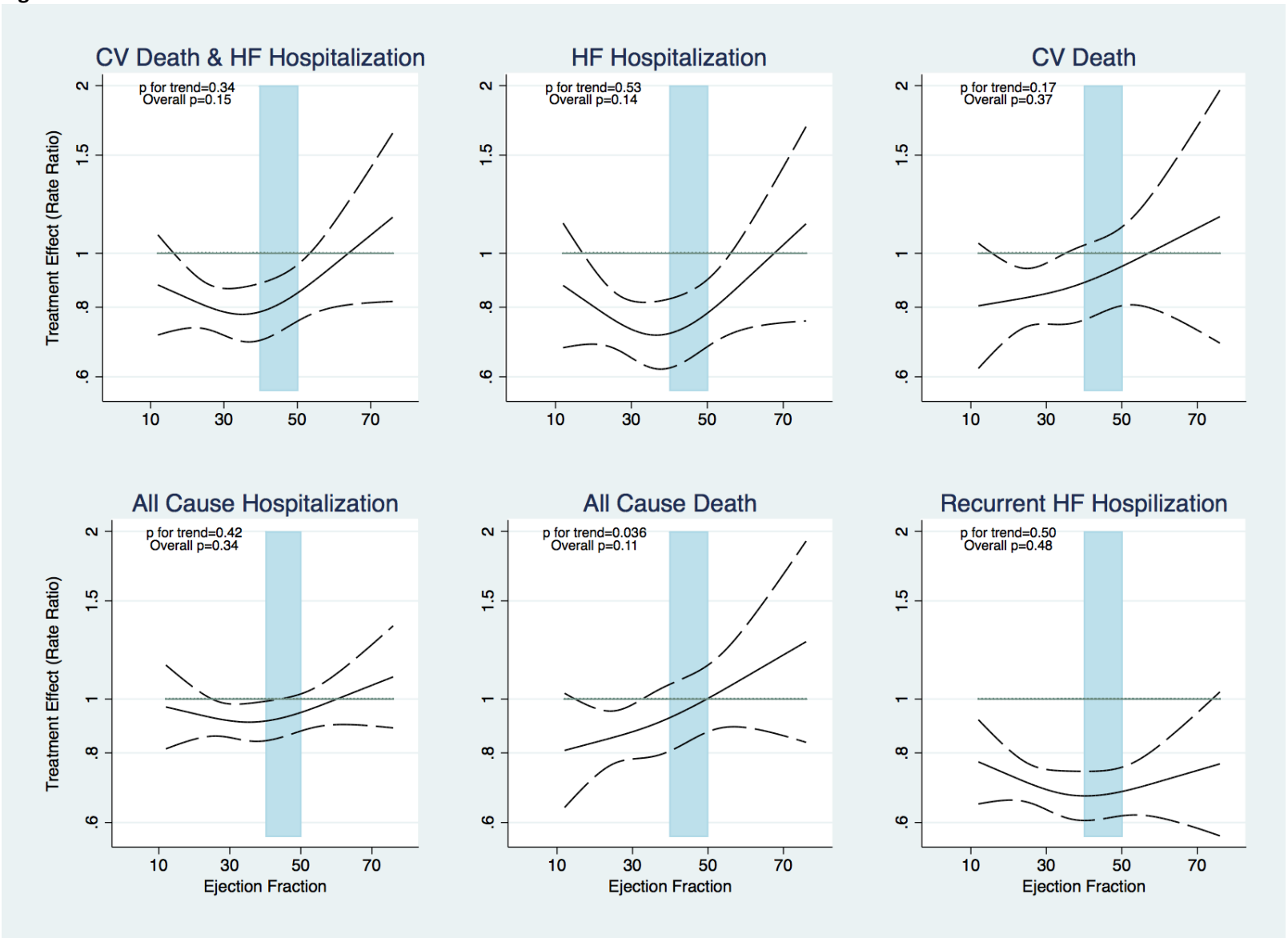

HFrEF: HR 0.82 (0.75-0.91) p<0.001
placebo
cande
p<0.001
placebo
cande
Years
Number at risk
Placebo 2167 1694 1429 1019
Candesartan 2155 1803 1547 1093
HFmrEF: HR 0.76 (0.61-0.96) p=0.02
placebo
cande
p=0.02
placebo
cande
Years
Number at risk
Placebo 655 568 522 320
Candesartan 667 608 559 349
HFpEF: HR 0.95 (0.79-1.14) p=0.57
placebo
cande
p=0.57
placebo
cande
Years
Number at risk
Placebo 973 861 775 465
Candesartan 980 874 788 480

**Figure 3**


CV Death & HF Hospitalization
p for trend=0.34
Overall p=0.15
HF Hospitalization
p for trend=0.53
Overall p=0.14
CV Death
p for trend=0.17
Overall p=0.37
All Cause Hospitalization
p for trend=0.42
Overall p=0.34
All Cause Death
p for trend=0.036
Overall p=0.11
Recurrent HF Hospilization
p for trend=0.50
Overall p=0.48
Treatment Effect (Rate Ratio)
.6
.8
1
1.5
2
10
30
50
70
Ejection Fraction